

NEW PROCESS FOR THE SYNTHESIS OF ENEAMIDE DERIVATIVES.

The present invention relates to a new process for the large-scale preparation of ene-amide derivatives useful as valuable substrates for asymmetric hydrogenation reaction and hence for the synthesis of enantiomerically pure amines derivatives known as key intermediates for active pharmaceuticals.

Several methods have been described in the prior art, for example in WO 99/18065 to prepare ene-amide precursors, but these methods are clearly not very general and unsuitable for large-scale production.

The articles JOC, 1998, 63, p 6084 of the authors M. Burk and Coll. and JOC, 1999, 64(6), p 1775 of the authors X. Zhang and Coll. describe a process for ene-amide compounds synthesis comprising the reduction of oxime derivatives with iron metal in presence of acetic anhydride/acetic acid or acetic anhydride only.

The US4194050 patent describes a process for ene-amide compounds synthesis comprising the reduction of oxime derivatives with ruthenium catalyst in presence of carboxylic anhydride.

However, these processes show some limitations such as product decomposition under these conditions, use of co-solvent to facilitate product isolation, impure ene-amides which required arduous purifications and low to moderate yields.

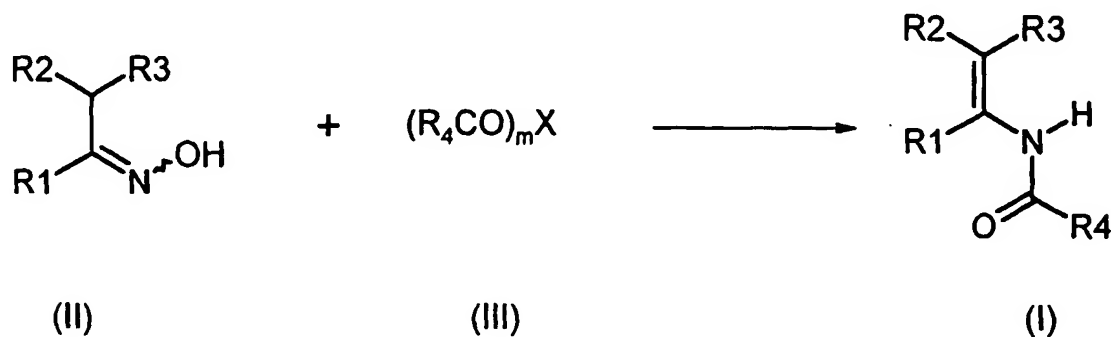
Prior art processes are unsuitable for large-scale production of ene-amide derivatives and hence not applicable to the commercial preparation of chiral amines via asymmetric hydrogenation.

The process according to the invention presents the advantages of obtaining ene-amides in good yields, great facility of product isolation, an excellent chemical purity of product and reproducible process.

5 The process according to the present invention is clearly suitable for the large-scale industrial production of amine derivatives, via an asymmetric or not hydrogenation reaction. These amine derivatives, asymmetric or not, are used as intermediates for active pharmaceuticals
10 preparation.

The present invention relates to a new process for the preparation of compounds of formula (I), comprising a hydrogenation-isomerization reaction of compound of formula (II) with an acyl derivative of formula (III) in presence of
15 a heterogeneous catalyst as shown in scheme (I).

scheme (I) :



20

wherein

R1 and R2 and R3 are independently a hydrogen atom, an alkyl, a cycloalkyl, a cycloalkylalkyl, an alkylaryl, an aryl, a heterocycle, a cyano, an alkoxy, an aryloxy, a
25 carboxyl, a carbamoyl, -CONR5R6 (in which R5 and R6 are independently an alkyl, arylalkyl, aryl group or R5 and R6 taken together may form a ring) or -COOR5 group (in which R5 is an alkyl, cycloalkyl, alkylaryl or aryl group), said

alkyl, cycloalkyl, cycloalkylalkyl, alkylaryl and aryl groups being substituted or not with a functional group or with R5;

5 or R1 and R2 taken together, may form a ring (which terms includes mono-, di- and higher polycyclic ring systems), said ring being substituted or not with a functional group or with R5;

10 R4 is a hydrogen atom, an alkyl, an aryl, an alkylaryl, said groups are substituted or not with a halogen atom as Cl, Br, or F;

X is an oxygen atom or a leaving group and

m is an integer 1 or 2;

when m is 1 then X is a leaving group; when m is 2 then X is a oxygen atom.

15

As used herein, unless the context otherwise requires:

20 The term "alkyl" preferably means a straight or branched alkyl group having 1 to 20 carbons atoms such as, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl optionally substituted with a functional group or with R5.

25 The term "cycloalkyl" preferably means a cycloalkyl group having 3 to 20 carbon atoms, such as, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl optionally substituted with a functional group or with R5.

30 The term "cycloalkylalkyl" preferably means a cycloalkylalkyl group having 3-20 carbon atoms such as but not limited to cyclopropylmethyl, cyclohexylmethyl optionally substituted with a functional group or with R5.

The term "aryl" preferably means an aryl group having 6 to 20 carbon atoms such as but not limited to phenyl, tolyl, xylyl, cumenyl, naphthyl optionally substituted with

a functional group or with an alkyl or with a fused aryl, or "aryl" means a heteroaryl group having 6 to 20 carbon atoms comprising one or more heteroatom as O, N or S such as, but not limited to, furyl, thienyl, pyrrolyl, imidazolyl, pyridyl, pyrazyl, pyrimidinyl, indolyl, carbazolyl, isoxazolyl, isothiazolyl optionally substituted with a functional group or with R5 or with an alkyl or with a fused aryl.

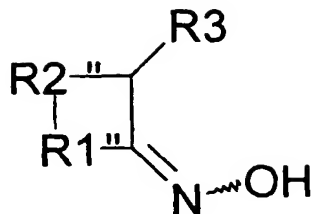
The term "alkylaryl" preferably means an alkylaryl group having 6 to 20 carbon atoms such as, but not limited to, benzyl, phenethyl, naphthylmethyl optionally substituted with a functional group or with R5.

The term "heterocycle" preferably means a heterocycle group having 6 to 20 carbon atoms comprising one more heteroatom as O, N or S such as but not limited to pyrrolidinyl, piperazinyl, piperidyl, imidazolidinyl, piperidyl, indolinyl, said heterocycle being saturated or not, said heterocycle being optionally substituted with a functional group or with R5 or a fused aryl group.

The term "functional group" means halogen atom, or a group comprising -OH, -OR5, -CN, -COOR5, -COR5, -CONR5R6, -OCOR5, -NH2, -NHR5, -NR5R6, -NO2, -SH, SR5, wherein R5 and R6 are independently an alkyl, an alkylaryl or an aryl group or R5 and R6 taken together may form a ring,

The term "leaving group" means preferably one of the groups -COR5, -CO2R5, -SO2R5, -COCCl3, -SO2F, -SO2CF3, -SO2CH2CF3, wherein R5 is an alkyl, an alkylaryl or an aryl group

The term "ring" preferably means the formation of ring having 4 to 30 carbon atoms, such as but not limited, compounds of formula hereunder

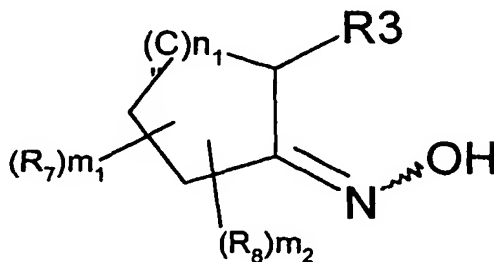


wherein -R1-R2- is a methylene, dimethylene, trimethylene, tetramethylene, pentamethylene or
 5 hexamethylene linkage optionally substituted with a functional group or a fused aryl..

The present invention is also relates to the most preferable compounds represented by the following formula:

10

formula (IIA)

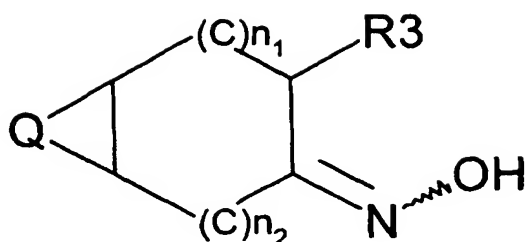


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wherein n1 is an integer from 0 to 4, m1 and m2 are each an integer from 0 to 4, R7 and R8 different or same, are an hydrogen atom, a functional group, an alkyl, an aryl, a cycloalkyl, an alkylaryl.

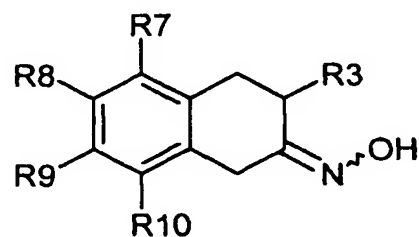
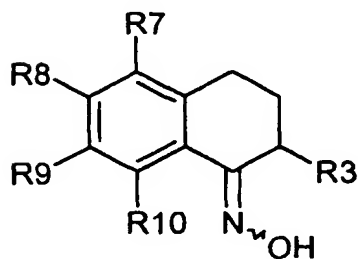
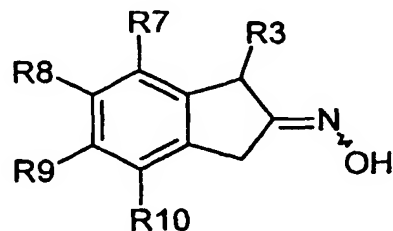
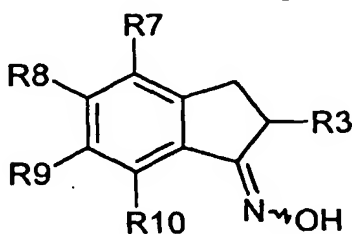
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formula (IIB)



wherein each n_1 and n_2 is an integer from 0 to 4, Q is
 5 an aryl, heteroaryl, cycloalkyl, heterocycloalkyl said group
 are substituted or not with at least one functional group
 preferably alpha- or beta-tetralone-oxime derivatives,
 alpha- or beta-indanone-oxime derivatives, substituted or
 not with a functional group.

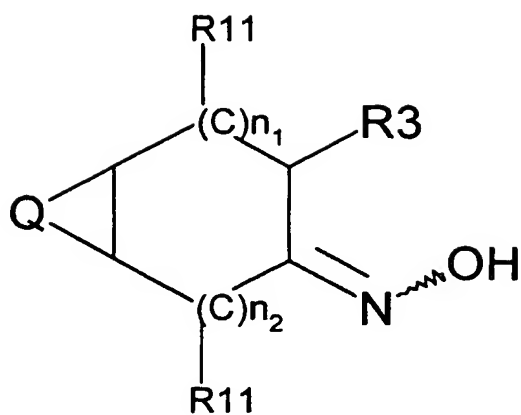
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15

Wherein R_3 , R_7 , R_8 are as defined above, R_9 , R_{10} are
 independently an hydrogen atom, a functional group, an
 alkyl, an aryl, a cycloalkyl, an alkylaryl.

Formula (IIC)

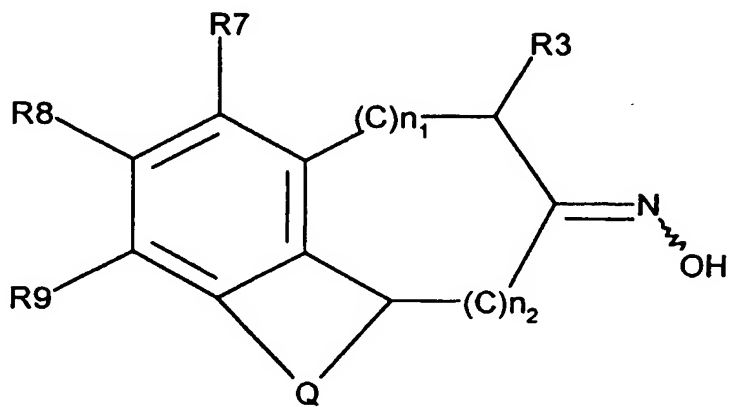


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wherein n1, n2, R3 and Q are as defined above, R11 is a hydrogen atom, an alkyl, an aryl.

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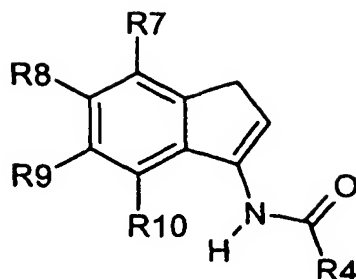
Formula (IID)



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wherein n1, n2, R3, R7, R8, R9 and Q are as defined above.

Formula (IIE)



wherein

5 R4 is a hydrogen atom, an alkyl, an aryl, an alkylaryl, said groups are substituted or not with a halogen atom as Cl, Br, or F;

 R7, R8, R9 and R10, identical or different, with not simultaneously an hydrogen atom, are an hydrogen atom, a
10 functional group, an alkyl, an aryl, preferably R7, R8 and R10 are an hydrogen atom, R9 is a methoxy and R4 is a methyl.

 The present invention relates also to the use of these
15 most preferable compounds in an hydrogenation reaction, asymmetric or not, giving an amine or amide derivative for pharmaceutical interest.

 Heterogeneous catalysts are based on metal like Pd,
20 Ir, Pt, Rh, Ni catalysts preferably Ir or Rh.

 The heterogeneous catalysts is used in the form of an oxide or metallic and may be supported on a suitable carrier (for example Ir/carbon, Ir/alumina, Rh/carbon or Rh/alumina).

25

 The method how to carry out the present invention will be explained hereinafter.

 The compound of formula (II) may be used as a syn-form, anti-form or a mixed-form of both.

The compound of formula (III) should be used in an amount of at least 2 molar equivalents for one molar equivalent of the oxime and may be used in a large amount as
5 a reacting agent combined with a solvent.

The amount of the catalyst used is in the range of 0.001 to 30% mol, for 1 mol of the oxime derivative.

10 The process of the present invention is carried out in a suitable solvent. Suitable solvents are aprotic non-basic solvents such as ethers (such as but not limited tetrahydrofuran, tetrahydropyran, diethyl ether, etc.) or
aromatic hydrocarbons (such as but not limited to benzene,
15 toluene, etc.) or carboxylic anhydrides or halogenated hydrocarbons or lower carboxylic acids or mixtures thereof.

The process of the present invention is carried out under a temperature range of -20 to 150 °C, preferably
20 between 20 °C to 120 °C.

The hydrogenation of the present invention is carried out under a hydrogen pressure between 0.5 to 20 bars.

25 The process of the present invention is carried out for a period of time in the range of 0.5 to 24 hours.

The process of the present invention can comprises a work up step of the organic solution of the compound of
30 formula (I) which is a washing step with water containing organic or mineral salts without halogen atom, preferably without chloride.

These organic or mineral salts can be selected among phosphate, sulfate, acetate, citrate, formate, borate, carbonate, ammonium, preferably phosphate.

5 The washing step allows to obtain a solution with a neutral pH. The isolated product is halogen ions free. These halogen ions can interfere with the catalyst during the subsequent asymmetric hydrogenation reaction and thus can affect the yield of this reaction. As a result, this
10 washing step allows to obtain a starting material of better quality for the next asymmetric hydrogenation reaction.

The invention will be better understood from the experimental details, which follow.

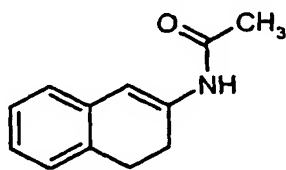
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Examples:

The present invention will be illustrated by the following examples, which will not limit the scope of the invention in any way.

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Example 1. Enamide from β -tétralone



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Example 1a. Enamide from β -tétralone with Rh /C

Into a 100 ml reactor are introduced tetrahydrofuran (43.5 ml) and 3,4-dihydro-1H-naphtalen-2-one oxime (7.2 g, 0.0447 mole). Then acetic anhydride (13.7 g, 0.134 mole) is added at 20-25°C over a period of 15 minutes. The suspension
30 is stirred for 1 hour and the catalyst 5% Rh/C (dry catalyst)(0.29 g, 4% by weight relative to oxime) is added.

The mixture is heated to 30°C and the hydrogen flow is started. Hydrogenation is continued over a period of 15 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and
5 the catalyst is washed with THF. This solution is added on a mixture of water (21 ml) and NaOH 30% (30.4 g) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

10

THF is distilled under reduced pressure, replaced by toluene and concentrated under vacuum to give an oily brown residue of *N*-(3,4-Dihydro-naphthalen-2-yl)-acetamide (6.14 g, 74 %).

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Example 1b. Enamide from β -tétralone with Ir /C

Into a 100 ml reactor are introduced tetrahydrofuran (43.5 ml) and 3,4-dihydro-1H-naphtalen-2-one oxime (7.2 g, 0.047 mole). Then acetic anhydride (13.5 g, 0.134 mole) is
20 added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Ir/C (dry catalyst)(0.29 g, 4% by weight relative to oxime) is added. The mixture is heated to 70°C and the hydrogen flow is started. Hydrogenation is continued over a period of 8 to 10
25 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (30 ml) and NaOH 30% (42 g) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes.
30 The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

THF is distilled under pressure, replaced by toluene and concentrated under vacuum to give an oily brown residue of N-(3,4-Dihydro-naphthalen-2-yl)-acetamide (5.5 g, 66 %).

5 Example 1c. Enamide from β -tétralone with Ir /C

5.5 g (0.0341 mol) of 3,4-dihydro-1H-naphtalene-2-one oxime was dissolved in 42 ml of THF. Then 9.66 ml of acetic anhydride was added dropwise. The reaction mixture is stirred at a temperature between 20-30 °C during 2 hours. To
10 this reaction mixture is added 0.44 g of the 5% Ir-carbon catalyts. Then the hydrogenation is carried out at a hydrogen pressure of 6 bars and at 75 °C during 3 hours. After the catalyst was filtered off, the filtrate was concentrated to dryness under reduced pressure. The residue
15 was dissolved in 120 ml of toluene and concentrated to dryness under reduced pressure. This new residue was recrystallized in a mixture of 10 ml of MTBE and 9 ml of hexane to obtain 3.82 g of the product, the compound N-(3,4-dihydro-naphtalene-2-yl)acetamide.

20

Crude yield: quantitative / Isolated yield: 59.9- %
Chemical purity (GC): 98.95 %.

Structural analysis

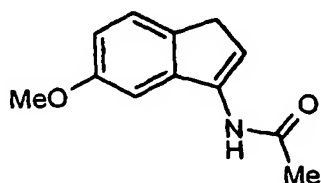
25 Oxime: 1H NMR (CDCl₃): 2.7-2.8 (t, 1H), 2.85-2.95 (t, 1H), 3-3.1 (m, 2H), 3.75 (s, 1H), 4.05 (s, 1H), 7.25-7.5 (m, 4H), 9.5 (m, OH).

Oxime acétate: 1H NMR (CDCl₃): 2.2 (s, 3H), 2.65-2.9 (m, 4H), 3.65 (s, 1H), 3.85 (s, 1H), 7.1-7.25 (m, 4H).

30 Enamide: * 1H NMR (CDCl₃): 2.3 (s, 3H), 2.6-2.75 (t, 2H), 3-3.15 (t, 2H), 7.15-7.35 (m, 5H), 7.75 (m, NH).

* 13C NMR (CDCl₃): 168, 134, 133, 132.5, 127, 126, 125.5, 125, 27.5, 27, 24.

Example 2: Enamide from 6-methoxy-1-indanone.



5 Example 2a . Enamide from 6-methoxy-1-indanone with Ir

/C

The reaction is carried out in the same manner as in example 1b, except that 1-indanone-oxime, methoxy-6- is used as starting material. The yield is 83.8 %.

10 The chemical purity is 98.4 %.

Example 2b . Enamide from 6-methoxy-1-indanone with Ir

/C.

15 Into a 100 ml reactor are introduced tetrahydrofuran (24 ml) and 6-Methoxy-1-indanone oxime (4.5 g, 0.0254 mole). Then acetic anhydride (7.78 g, 0.0762 mole) is added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Ir/C (dry catalyst)(0.225 g, 4% by weight relative to oxime) is added. The mixture is

20 heated to 70-75°C and the hydrogen flow is started. Hydrogenation is continued over a period of 1 to 2 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a

25 mixture of water (15 ml) and NaOH 30% (13 ml) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

The organic layer is concentrated under vacuum at 50°C to give brown crystals of *N*-(6-Methoxy-3*H*-inden-1-yl)-acetamide (3.34 g, 70 %).

5 Example 2c. Enamide from 6-methoxy-1-indanone with Rh
 /C

 Into a 100 ml reactor are introduced tetrahydrofuran (24 ml) and 6-Methoxy-1-indanone oxime (4.5 g, 0.0254 mole). Then acetic anhydride (7.78 gr, 0.0762 mole) is added at 20-
10 25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Rh/C (dry catalyst) (0.225 g, 4% by weight relative to oxime) is added. The mixture is heated to 30-35°C and the hydrogen flow is started. Hydrogenation is continued over a period of 7 to 8 hours
15 under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (15 ml) and NaOH 30% (13 ml) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes.
20 The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

 The organic layer is concentrated under vacuum at 50°C to give off-white crystals of *N*-(6-Methoxy-3*H*-inden-1-yl)-acetamide (3.82 g, 80 %).

25

Example 2d. Enamide from 6-methoxy-1-indanone with
 Rh/C

 Into a 250 ml reactor are introduced tetrahydrofuran (50 ml) and 1-indanone-oxime, methoxy-6- (10 g, 0.056 mole).
30 Then acetic anhydride (17.3 g, 0.170 mole) is added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Rh/C (dry catalyst) (0.40 g, 4% by weight relative to oxime) is added, rinsed by tetrahydrofuran (10 ml). The mixture is heated to 30°C and

the hydrogen flow is started. Hydrogenation is continued over a period of 15 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (29 ml) and NaOH 30% (42.2 g) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with a buffer solution of sodium dihydrogen phosphate (37.8 w/w) adjusted at pH 6 with NaOH 30%.

THF is distilled under reduced pressure, replaced by toluene and concentrated under vacuum to give an oily brown residue of *N*-(6-Methoxy-3*H*-inden-1-yl)-acetamide (6.6 g, 57.5 %).

15 Structural analysis

Oxime: * ¹H NMR 270MHz JEOL (DMSO): 2.7-2.95 (m, 4H), 3.75 (s, 3H), 6.9 (m, 1H), 7 (m, 1H), 7.25 (d, 1H), 10.8 (s, OH).

20 * ¹³C NMR (DMSO): δ 165, 162, 150, 147, 137, 127, 112, 67, 34, 32.

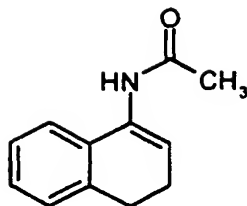
Oxime acetate: * ¹H NMR (CDCl₃): 2.15 (s, 3H), 2.95 (m, 4H), 3.7 (s, 3H), 6.85-6.95 (m, 1H), 7.1-7.15 (m, 1H), 7.25 (m, 1H).

25 * ¹³C NMR (CDCl₃): 171, 168, 158, 143, 135, 126, 122, 105, 56, 29, 28, 19.

Enamide: * ¹H NMR (CDCl₃): 3 (s, 3H), 3.6 (s, 3H), 4.1 (d, 2H), 7.5-7.6 (dd, 1H), 7.65 (m, 2H), 8.05-8.15 (d, 1H), 8.45 (s, 1H).

30 * ¹³C NMR (CDCl₃): 169, 158, 140, 136, 134, 123, 117, 110, 103, 55, 35, 23.

Example 3: Enamide from α-tétralone.



Example 3a. Enamide from α -tétralone with Rh /C

Into a 180 ml reactor are introduced tetrahydrofuran (60 ml) and 3,4-dihydro-2H-naphtalen-1-one oxime (10 g, 0.062 mole). Then acetic anhydride (19 g, 0.186 mole) is added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Rh/C (dry catalyst)(0.4 g, 4% by weight relative to oxime) is added. The mixture is heated to 30°C and the hydrogen flow is started. Hydrogenation is continued over a period of 15 to 20 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (30 ml) and NaOH 30% (42 g) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

THF is distilled under reduced pressure and replaced by toluene; the suspension is stirred at 5°C for 1 hour then the precipitate is filtered off and washed twice with 10 ml of cold toluene.

Crystals are dried under vacuum at 50°C to give N(3,4-dihydro-1-naphtalenyl)Acetamide (9.74 g, 84%).

Example 3b. Enamide from α -tétralone with Ir /C

Into a 180 ml reactor are introduced tetrahydrofuran (60 ml) and 3,4-dihydro-2H-naphtalen-1-one oxime (10 g, 0.062 mole). Then acetic anhydride (19 g, 0.186 mole) is added at

20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Ir/C (dry catalyst)(0.4 g, 4% by weight relative to oxime) is added. The mixture is heated to 70°C and the hydrogen flow is started. Hydrogenation is continued over a period of 4 to 5 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (30 ml) and NaOH 30% (42 g) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

THF is distilled under reduced pressure and replaced by toluene; the suspension is stirred at 5°C for 1 hour then the precipitate is filtered off and washed twice with 10 ml of cold toluene.

Crystals are dried under vacuum at 50°C to give N(3,4-dihydro-1-naphtalenyl) Acetamide (9.18 g, 79%).

Structural analysis

Oxime: * ¹H NMR 270MHz JEOL (DMSO): 1.65-1.8 (m, 2H), 2.6-2.8 (m, 4H), 7.1-7.3 (m, 3H), 7.8-7.95 (d, J = 7.5 Hz, 1H), 11.1 (s, OH).

* ¹³C NMR (DMSO): δ 152.5, 137, 132, 129, 128, 126, 123, 29, 23, 21.

Oxime acetate: * ¹H NMR (CDCl₃): 2.75-3.85 (m, 2H), 3.2 (s, 3H), 3.65-3.75 (m, 2H), 3.75-3.85 (m, 2H), 8.05-8.3 (m, 3H), 9.05-9.1 (d, 1H).

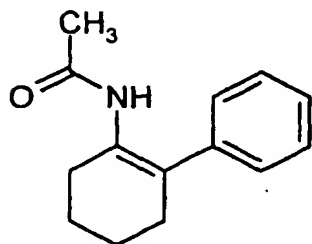
* ¹³C NMR (CDCl₃): 169, 162, 141, 131, 128, 127.5, 127, 126, 29, 26, 22, 20.

Enamide: * ¹H NMR (CDCl₃): 2.1 (s, 3H), 2.25-2.45 (m, 2H), 2.65-2.85 (m, 2H), 6.3 (t, 1H), 7.05-7.35 (m, 4H).

* ^{13}C NMR (CDCl_3): 169, 137, 132, 127.5, 127, 126, 121, 120, 28, 24, 22.5.

Example 4: Enamide from 2-Phenylcyclohexanone.

5



Example 4a: Enamide from 2-Phenylcyclohexanone with Ir
/C

10 Into a 100 ml reactor are introduced tetrahydrofuran (24 ml) and 2-phenylcyclohexanone oxime (4 g, 0.0211 mole). Then acetic anhydride (6.47 g, 0.0634 mole) is added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Ir/C (dry catalyst)(0.16 g,
15 4% by weight relative to oxime) is added. The mixture is heated to 70°C and the hydrogen flow is started. Hydrogenation is continued over a period of 2.5 to 3 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and
20 the catalyst is washed with THF. This solution is added on a mixture of water (12 ml) and NaOH 30% (10.8 ml) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

25

The organic layer is concentrated under vacuum at 50°C to give an oily white residue of *N*-(2-Phenyl-cyclohex-1-enyl)-acetamide (3.5 g, 77 %).

Example 4b. Enamide from 2-Phenylcyclohexanone with Rh

/C

Into a 100 ml reactor are introduced tetrahydrofuran (24 ml) and 2-phenylcyclohexanone oxime (4 g, 0.0211 mole).
5 Then acetic anhydride (6.47 g, 0.0634 mole) is added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Rh/C (dry catalyst) (0.16 g, 4% by weight relative to oxime) is added. The mixture is heated to 25-30°C and the hydrogen flow is started.
10 Hydrogenation is continued over a period of 5 to 6 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (12 ml) and NaOH 30% (10.8 ml) at 5°C over
15 a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

The organic layer is concentrated under vacuum at 50°C
20 to give white crystals of N-(2-Phenyl-cyclohex-1-enyl)-acetamide (3.86 g, 85 %).

Structural analysis

Oxime: ¹H NMR (DMSO): 1.4-1.65 (m, 2H), 1.7-1.8 (m, 2H), 1.9-2.2 (m, 3H), 2.8-2.95 (m, 1H), 4.1-4.5 (m, 1H), 7.1-7.4 (m, 5H).

Oxime acetate: * ¹H NMR (CDCl₃): 1.55-1.75 (m, 4H), 1.85-2.1 (m, 1H), 2.15 (s, 3H), 2.17-2.3 (m, 1H), 2.4-30 2.5 (m, 1H), 2.75-2.87 (m, 1H), 3.85-3.91 (t, 1H), 7.15-7.4 (m, 5H).

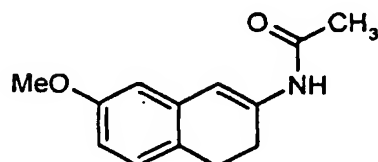
* ¹³C NMR (CDCl₃): 195, 170, 169, 138, 128, 127.5, 126, 46, 31, 27, 25, 22.5, 20.

Enamide: * ^1H NMR (CDCl_3): 1.65-1.8 (m, 4H), 2.3 (s, 2H), 2.6 (s, 2H), 6.55 (s, NH), 7.1-7.4 (m, 5H).

* ^{13}C NMR (CDCl_3): 167, 141, 131, 128, 127.5, 126.5, 126, 31, 27.5, 24, 22.5.

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Example 5: Enamide from 2-methoxy-7-tétralone.



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Enamide from 2-methoxy-7-tétralone with Rh /C

Into a 100 ml reactor are introduced tetrahydrofuran (24 ml) and 2-Methoxy-7-tetralone oxime (4.5 g, 0.0235 mole). Then acetic anhydride (7.21 gr, 0.0706 mole) is added at 20-25°C over a period of 15 minutes. The suspension is stirred for 1 hour and the catalyst 5% Rh/C (dry catalyst)(0.18 gr, 4% by weight relative to oxime) is added. The mixture is heated to 30-35°C and the hydrogen flow is started. Hydrogenation is continued over a period of 4 to 5 hours under 4 bars hydrogen pressure. After the end of the reaction, the suspension is filtered from the catalyst and the catalyst is washed with THF. This solution is added on a mixture of water (14 ml) and NaOH 30% (12 ml) at 5°C over a period of 1 hour and maintained at 20°C during 30 minutes. The aqueous phase is discarded and the organic layer is washed with water saturated with NaCl.

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The organic layer is concentrated under vacuum at 50°C to give grey crystals of N-(7-Methoxy-3,4-dihydro-naphthalen-2-yl)-acetamide (4.21 g, 82.5 %).

Structural analysis

Oxime : ¹H NMR (CDCl₃): 2.7-2.8 (t, 1H), 2.85-2.95 (t, 1H), 3.45 (s, 2H), 3.75 (s, 3H), 6.65 (m, 2H), 7.1(m, 1H), 10.05 (s, OH)

5 Oxime acetate: Non-isolated

Enamide :¹H NMR (CDCl₃): 2.1 (s, 3H), 2.35-2.45 (t, 2H), 2.7-2.85 (t, 2H), 3.75 (s, 3H), 6.6 (m, 2H), 6.95 (m, 1H), 7.1 (s, 1H), 7.35 (m, NH)

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